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Influence of inter-stimulus interval of spinal cord stimulation in patients with disorders of consciousness: A preliminary functional near-infrared spectroscopy study

Yujin Zhang[a,b,1], Yi Yang[c,1], Juanning Si[a,b], Xiaoyu Xia[c], Jianghong He[c,*], Tianzi Jiang[a,b,d,e,f,**]

[a] Brainnetome Center, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China
[b] National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China
[c] Department of Neurosurgery, PLA Army General Hospital, Beijing 100700, China
[d] Key Laboratory for NeuroInformation of the Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 625014, China
[e] CAS Center for Excellence in Brain Science, Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China
[f] Queensland Brain Institute, University of Queensland, St. Lucia, Queensland 4072, Australia

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A B S T R A C T

Spinal cord stimulation (SCS) is a promising treatment for disorders of consciousness (DOC), but the underlying mechanism and most effective procedures remain uncertain. To optimize the protocol, previous studies evaluated the frequency-specific effects of SCS on neurophysiological activities. However, whether and how the inter-stimulus interval (ISI) parameter affects the SCS neuromodulation in DOC remains unknown. We enrolled nine DOC patients who had implanted SCS devices and conducted three different durations of ISIs. Using functional near-infrared spectroscopy (fNIRS), we monitored the blood volume fluctuations in the prefrontal and occipital cortices during the SCS. The results showed that short stimuli (30 s) induced significant cerebral blood volume changes, especially in the prefrontal cortex, an important area in the consciousness system. By comparing the mean value of the responses from the first and the last block in each session, a shorter ISI was found to improve the blood volume in the prefrontal cortex. This phenomenon was more significant for the subgroup of patients with a favorable prognosis. These preliminary results imply that the ISI may be an important factor for SCS. The research paradigm proposed here also provides insights for further quantitative evaluations of the therapeutic effects of neuromodulation.

1. Introduction

With great advancements in the emergency care of brain injury, the number of patients with disorders of consciousness (DOC), including the minimally conscious state (MCS) and the vegetative state (VS), has significantly increased (Georgiopoulos et al., 2010; Laureys et al., 2004). However, there is no effective evidence-based procedure for awakening or clinically assessing patients with DOC (Della Pepa et al., 2013; Georgiopoulos et al., 2010).

Alongside a variety of pharmacologic and non-pharmacologic interventions, neuromodulation techniques, such as deep brain stimulation (DBS) (Schiff et al., 2007) and spinal cord stimulation (SCS) (Kanno et al., 2009; Yamamoto et al., 2013; Yamamoto et al., 2012), have been used in the treatment of DOC patients. These techniques intervene directly in the central nervous system to improve the arousal and awareness system (e.g. the mesocircuit) (Della Pepa et al., 2013; Giacino et al., 2014; Guerra et al., 2014). Specifically, SCS utilizes a surgically implanted electrode in the epidural space (at C2-C4) to stimulate the ascending reticular activating system (ARAS) and regulate the awareness circuit (Della Pepa et al., 2013). Although experiments

Abbreviations: ARAS, ascending reticular activating system; CBF, cerebral blood flow; DBS, deep brain stimulation; DOC, disorders of consciousness; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; FWHM, full-width-at-half-maximum; GOS, Glasgow Outcome Scale; HbO, oxygenated hemoglobin; HbR, deoxygenated hemoglobin; HbT, total hemoglobin; ISI, inter-stimulus interval; JFKCRS-R, JFK Coma Recovery Scale; LTP, long-term potentiation; MBLL, modified Beer-Lambert law; MCS, minimally conscious state; MSN, medium spiny neuron; rCBV, regional cerebral blood volume; SCS, spinal cord stimulation; TMS, transcranial magnetic stimulation; VS, vegetative state

* Corresponding author.
** Correspondence to: T. Jiang, 95 Zhongguancun East Road, 100190 Beijing, China.
E-mail addresses: he_jianghong@sina.cn (J. He), jiangtz@nlpr.ia.ac.cn (T. Jiang).
[1] The authors contributed equally to this work.

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applying SCS to DOC have been few, the prior literature has shown some encouraging effects. The first study investigating the effects of SCS on VS patients reported that 33.3% (2 out of 6) patients displayed clinical improvement (recovered from the vegetative syndrome) (Funahashi et al., 1989). After a few decades, the improvement rate from VS patients after using SCS has been greatly improved to 54% (109 out of 201) (Kanno et al., 2009). As reported by Yamamoto, 70% (7 out of 10) of the patients had recovered from MCS following SCS therapy: they were able to carry out complete functional interactive communication consistently and reliably, and/or demonstrate the functional use of two different objects (Yamamoto et al., 2012). Compared to DBS, SCS is more cost-effective and less invasive with lower risk. SCS is also more feasible and has fewer limitations involving surgical instruments or the patients' condition.

SCS has been found to enhance global cerebral blood flow (CBF) and cerebral glucose metabolism by regulating the sympathetic system (Della Pepa et al., 2013; Visocchi et al., 2011). For instance, CBF can increase by an average of about 22% after SCS (Liu et al., 2008; Yamamoto et al., 2012). In addition, SCS has been found to promote the release of neurotransmitters and neuromodulators, such as dopamine and norepinephrine (but not epinephrine) (Georgiopoulos et al., 2010; Kaplitt, 2013; Liu et al., 2008; Visocchi et al., 2011), and to improve the nerve conduction and electrical activity of the cerebral cortex (Della Pepa et al., 2013; Kaplitt, 2013; Visocchi et al., 2011). However, these pioneering studies primarily focused on global-level effects; the link between consciousness and higher brain activity has not been completely determined.

Designing the parameters, especially the amplitude, frequency, pulse width, continuous or intermittent stimulation pattern, and the inter-stimulus interval (ISI), is a vital step for optimizing neuromodulation therapy using stimulation. Low frequencies (10–40 Hz) are known to induce excitation of neuronal populations, whereas high frequencies (> 60 Hz) inhibit them (Guerra et al., 2014; Yampolsky et al., 2012). However, except of frequency, the other parameters have seldom been investigated. As a matter of fact, designating the parameters in clinical is still primarily based on clinical observations, behavioral evaluations, and chief complaint. But the last one cannot be obtained for patients with DOC because of the lack of consciousness. Actually, which are the best parameters for the patient is still a question. Therefore, it is essential for developing a reliable quantitative evaluation system to assess the effects of neuromodulation and to provide guidance for designing the best parameters, especially for therapy for patients with DOC, who cannot give any subjective feedback. A quantitative evaluation is also essential for developing a closed-loop neuromodulation system. Finding the optimal ISI length (the length of the resting state period after each stimulation period) is, of all the parameters, the one that is most needed to prevent fatigue and damage to the neurons due to excessive continuous stimulation. In fact, the length of the interval between consecutive stimuli has been found to greatly affect the reactivity and persistence of neurons (Huettel et al., 2004; Zhang et al., 2008), but an investigation into different ISIs of the SCS has not yet been done in patients with DOC. Do different ISIs produce different effects? What ISI design is the most appropriate for SCS? To address these issues, it is necessary to investigate the influence of different ISIs of SCS quantitatively.

Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are traditional techniques for measuring brain responses (Bruno et al., 2011; Jox et al., 2012). However, neither of these techniques is suitable for assessing real-time brain responses during SCS processing. However, functional near infrared spectroscopy (fNIRS) (Jobsis, 1977), a non-invasive optical neuroimaging technique, is more tolerant of movement artifacts and metal implants than fMRI, is superior to EEG in localizing and segmenting brain regions, and is not subject to interference from electrical stimulation. In addition, fNIRS is cost-effective and portable and can be used in a clinical environment, making it uniquely suitable for longitudinal monitoring and repeated experiments during SCS. Moreover, because fNIRS provides information about multiple specific physiological variables (e.g., the deoxygenated (HbR), oxygenated (HbO), and total (HbT) hemoglobin) (Zeff et al., 2007), it can provide a relatively comprehensive understanding of the hemodynamic changes during SCS. As mentioned above, fNIRS has potential to play a vital role in assessing the real-time modulation of SCS.

In this study, we measured hemodynamic activity using a multiple-channels fNIRS technique in patients with DOC during block-designed SCS with various ISIs. Our research goals were two-fold: to provide insight into the fundamental mechanism of SCS for patients with DOC and to quantitatively assess the neuromodulation effects of different ISIs of SCS to provide some guidance for designing the optimal parameters for SCS.

2. Materials and methods

2.1. Participants

Nine patients (5 males and 4 females, ages 17–64 years) with DOC were recruited from the Department of Neurosurgery, PLA Army General Hospital for this study. The clinical data for all the patients are provided in Table 1. Each patient had had an implanted SCS device (3587A, Medtronic Inc., Minneapolis, Minnesota, USA, as shown in Fig. 1) for about 1 month but had not yet received any SCS treatment. Their consciousness state was assessed twice, before and 1 month after SCS surgery, using the JFK Coma Recovery Scale (JFK CRS-R) (Giacino, 2004). In addition, their prognosis was assessed using the Glasgow Outcome Scale (GOS) at 6 months after SCS surgery. GOS provides a measurement of outcome ranging from 1 to 5 (1, dead; 2, vegetative state/severe disability; 3, able to follow commands/unable to live independently/moderate disability; 4, able to live independently/unable to return to work or school; 5, good recovery/able to return to work or school) (Jennett and Bond, 1975). In this study, any GOS score less than or equal to 2 was defined as "unfavorable prognosis", whereas a score from 3 to 5 was defined as "favorable prognosis" (PVS TM-STFo, 1994). No other treatments, including drugs that could modify cortical excitability, were administered. Written informed consent for each subject in the study was obtained from the patient's caregivers. The present study was approved by the ethics committee of the PLA Army General Hospital (No2015-026).

2.2. Study design

In this study, all the patients received 70 Hz (Bai et al., 2017; Kanno et al., 2009) SCS with a pulse width of 210 μs. The intensity was between 1.0 V and 5.0 V, depending on the patient's tolerance. According to our preliminary results in two pre-experiments with different time lengths for SCS "On" and "Off" periods (see Appendix A), we found the hemodynamic activity changed noticeably within a short period (30 s) during SCS and returned to the baseline in 60 s–90 s. Therefore, to control the overall length of the experiment and to ensure the comfort of the patients, the duration of the SCS was set at 30 s, which was enough to evoke a reliable hemodynamic response. The ISI was set at three levels, each of which was longer than 90 s: 2 min (short), 3 min (medium) and 5 min (long), as shown in Fig. 2 (a). To reduce the noise/artifacts, we repeated the stimulation four times. The SCS was turned off during the ISI "Off" period. The three different ISIs were presented in a pseudo-random order. Between each pair of sessions, the patients were given a 30 min rest to avoid superimposed effects. All the patients underwent the experimental protocol on up to three different days. To eliminate sequence effects, each of the three sessions used a different sequence of ISIs. All the experiments were carried out in a quiet, dimly illuminated, acoustically shielded room.